PATENT
Attorney Docket No. 05558.0026.CPUS03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Jane A. Gross *et al.*	Title:	SOLUBLE RECEPTORS BR32X2 AND METHODS OF USING
App. No.:	09/627,206	Art Unit:	1645
Conf. No.:	1238	Examiner:	Robert A. Zeman
Filing Date:	July 27, 2000		

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Mail Stop: Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants submit this Appeal Brief under 37 CFR § 41.37 to the Board of Patent Appeals and Interferences in response to the Final Office Action mailed October 27, 2009, the Advisory Action mailed March 25, 2010, and in view of the Notice of Appeal filed January 27, 2010 for the above-identified patent application. Submitted herewith is a petition for a one-month extension of time under 37 C.F.R. § 1.17(a)(1), along with the requisite fee. Thus, this reply is timely filed.

The Commissioner is hereby authorized to deduct the filing fee of $540 as well as any other fee that may be deemed necessary and proper from Howrey LLP Deposit Account No. 08-3038, referencing the above-identified docket number.

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1. Real Party in Interest

The real party in interest is ZymoGenetics, Inc., having a place of business at 1201 Eastlake Avenue East, Seattle, WA 98102. An assignment of the application to the real party in interest was recorded at Reel 012117, Frame 0067.

2. Related Appeals and Interferences

Appellants bring to the attention of the Examiner that a Notice of Appeal was filed on January 27, 2010 in connection with co-pending U.S. Application No. 09/569,245, filed May 11, 2000.

3. Status of Claims

As of the Final Rejection mailed October 27, 2009 and the Advisory Action mailed March 25, 2010, claims 107-111 and 122-132 are pending in the application, all of which were rejected in the Final Rejection mailed October 27, 2009 and these rejections were maintained in the Advisory Action dated March 25, 2010. Claims 1-106 and 112-121 have been canceled.

The rejections of claims 107-111 and 122-132 are hereby being appealed.

4. Status of Amendments

An amendment was filed subsequent to the mailing of a Final Rejection and on the same day as the filing of a Notice of Appeal. The amendment, filed January 27, 2010, proposed to amend claims 122, 124, 125, and 127-129 and proposed to cancel claims 117-121. An Advisory Action and Notice of Non-Compliant Amendment were mailed on March 5, 2010 informing Appellants that the proposed amendments were not in compliance with 37 C.F.R. 1.121 and therefore were not entered. A response to the Advisory Action and Notice of Non-Compliant Amendment was subsequently filed proposing to amend claims 122, 124, 125 and 127-129 and proposing to cancel claims 112-121. The Examiner indicated that the amendments will be entered for purposes of appeal.

The appending claims are believed to be an accurate listing of the claims under appeal.

5. Summary of Claimed Subject Matter

Independent claim 107, now under appeal, recites a method of inhibiting B lymphocyte proliferation in a mammal comprising administering to the mammal a composition comprising a fusion protein that consists of a first portion and a second portion joined by a peptide bond wherein:

- The first portion consists of the sequence of amino acids 25-104 of SEQ ID NO: 6, and
- The second portion is an immunoglobulin heavy chain constant region, and wherein
- The fusion protein binds ztnf4

The subject matter of independent claim 107 is fully supported by the entire specification as filed. The use of fusion proteins consisting of a first portion having the sequence of amino acids 25-104 of SEQ ID NO: 6 joined by a peptide bond to a second portion in a method of inhibiting ztn4 activity in a mammal is described at page 3, lines 8-18. Page 4, lines 3-5, specifies that the second portion is an immunoglobulin heavy chain constant region. The specification describes B lymphocyte proliferation as a type of ztn4-related activity that may be inhibited at page 9, lines 10-11 and page 58, lines 1-13. The specification explains how the fusion proteins can obtained by, *inter alia*, production in genetically engineered host cells and subsequent isolation or chemical synthesis according to conventional techniques at pages 36-52. The specification, at example 3 (page 92, line 20 to page 95, line 19), describes an assay by which the effect of such fusion proteins on lymphocyte proliferation can be tested. Specific dosages and

administration routes by which such fusion proteins may be administered to a mammal are described at pages 88-90.

Claim 108 depends from claim 107 and specifies that the immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region. The subject matter of this claim is fully supported by the specification as filed at page 100, lines 10-14.

Claim 109 depends from claim 108 and specifies that the immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region of IgG1. The subject matter of this claim is fully supported by the specification as filed at page 100, lines 10-14.

Claim 110 depends from claim 107 and specifies that the composition comprises multimeric proteins comprising one or more polypeptide fusions. The subject matter of this claim is fully supported by the specification as filed at page 50, lines 19-30.

Claim 111 depends from claim 110 and specifies that the composition comprises dimeric proteins comprising one or more polypeptide fusions. The subject matter of this claim is fully supported by the specification as filed at page 50, lines 19-30.

Claim 122 depends from claim 107 and specifies that the B lymphocyte proliferation is associated with an autoimmune disease. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 16 to 22 and page 59, lines 21-26.

Claim 123 depends from claim 122 and specifies that the autoimmune disease is systemic lupus erythematosus, myasthenia gravis, multiple sclerosis or rheumatoid

arthritis. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 23-26.

Claim 124 depends from claim 107 and specifies that the B lymphocyte proliferation is associated with bronchitis, emphysema or end stage renal failure. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 27-28.

Claim 125 depends from claim 107 and specifies that the B lymphocyte proliferation is associated with renal disease. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 29-30.

Claim 126 depends from claim 125 and specifies that the renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 31-33.

Claim 127 depends from claim 107 and specifies that the B lymphocyte proliferation is associated with renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis. The subject matter of this claim is fully supported by the specification as filed at page 4, lines 34-36.

Claim 128 depends from claim 107 and specifies that inhibiting B lymphocyte proliferation is associated with regulation of immune response. The subject matter of this claim is fully supported by the specification as filed at page 5, lines 3 to 4.

Claim 129 depends from claim 107 and specifies that inhibiting B lymphocyte proliferation is associated with immunosuppression. The subject matter of this claim is fully supported by the specification as filed at page 5, lines 4-6.

Claim 130 depends from claim 129 and specifies that the immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation. The subject matter of this claim is fully supported by the specification as filed at page 5, lines 6-8.

Claim 131 depends from claim 130 and specifies that the autoimmune disease is insulin dependent diabetes mellitus or Crohn's Disease. The subject matter of this claim is fully supported by the specification as filed at page 5, lines 10-12.

Claim 132 depends from claim 130 and specifies that the inflammation is associated with joint pain, swelling, anemia or septic shock. The subject matter of this claim is fully supported by the specification as filed at page 5, lines 14-16.

6. Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection to be reviewed on appeal are as follows:

(a) Whether claims 107-111 and 122-132 are unpatentable under 35 U.S.C. § 103(a) over Bram *et al.* (WO 98/39361) (hereinafter *"Bram WO"*) in view of Presta *et al.* (U.S. Patent No. 5,739,277) (hereinafter *"Presta"*)

(b) Whether claims 107-111 and 122-132 are unpatentable under 35 U.S.C. § 103(a) over Bram *et al.* (US Patent No. 5,969,102) (hereinafter *"Bram US"*) in view of *Presta.*

A copy of each of the Bram WO, Bram US and Presta publications is provided under the Evidence Appendix.

7. Argument

I. The Rejections Under 35 U.S.C. § 103(a) Over *Bram WO* in View of *Presta* Are Improper and Should Be Withdrawn

The Examiner, in the Advisory Action mailed March 25, 2010 (hereinafter the "March 25 Advisory Action"), characterizes the claims currently under appeal as "drawn to methods of inhibiting B cell proliferation by the administration of a composition comprising a fusion protein that consists of a first and second portion joined by a peptide bond wherein the first portion consists of the amino acid sequence of amino acid 25 to 104 of SEQ ID NO:6 or residues 1 to 154 of SEQ ID NO:6 and wherein the second portion is a heavy chain constant region of human immunoglobulins (e.g. IgG1) and wherein the fusion protein binds ztnf4." Appellants would like to clarify that the amendments proposed in the Response to Non-compliant Amendment filed March 11, 2010 have been entered by the Examiner, as indicated under the "Amendments" heading in the March 25 Advisory Action. Accordingly, the claims under appeal are drawn only to methods of inhibiting B cell proliferation by administration of a composition comprising a fusion protein that consists of a first portion consisting of the amino acid sequence of amino acids 25 to 104 of SEQ ID NO:6. Methods employing administration of fusion proteins having a first portion consisting of the amino acid sequence of residues 1 to 154 of SEQ ID NO:6 were the subject of claim 117 which has been canceled.

The Examiner, in rejecting claims 107-111 and 122-132, alleges that *Bram WO* teaches (1) genetically engineered constructs to regulate B-cell activity through interaction with cellular receptor ligands (2) that such constructs can consist of the extracellular domain of the TACI receptor linked by a peptide bond to the Fc domain of

an immunoglobulin (3) that the extracellular domain of the TACI receptor has the amino acid sequence corresponding to about residue 1 to about residue 166 of the TACI sequence and (4) that the ligand binding region is a sub-fragment of the extracellular domain. Therefore, according to the Examiner, by utilizing the methods and materials disclosed by *Bram WO*, "one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf is an endogenous ligand of TACI…Moreover, since the fusion proteins disclosed by Bram et al. are **identical** to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention." March 25 Advisory Action, p. 7 (emphasis added). According to the Examiner, *Bram WO* fails to disclose the specific use of IgG1 heavy chains in fusion proteins or TACI extracellular sub-fragments consisting of amino acid residues 25-104 or 1-154 of SEQ ID NO:6 in fusion proteins. The Examiner refers to *Presta* as disclosing "methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)." According to the Examiner:

> …given that there (sic) Bram discloses the use of the full length TACI extracellular domain (SEQ ID NO:6) and that there are a finite number of fragments of said extracellular domain and (sic) it would have been obvious to the skilled artisan to produce said fragments in order to identify the specific binding domain (fragment) of the TACI extracellular domain responsible for the observed biological activity (i.e. modulating B cell proliferation/activity). The skilled person would have had a reasonable expectation of success as the generation of protein fragments to identify biologically active domains…It would have been obvious for one of ordinary skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation)

> by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. March 25 Advisory Action, pages 7-8.

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness in rejecting claims under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the Examiner must provide a clear articulation of the reasons why the claimed invention would have been obvious, i.e., the Examiner must provide a reason one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. *See* MPEP § 2143.02. Finally, "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981 (CCPA 1974). The expectation of success must be found in the prior art, not the applicant's disclosure. *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988). Only if this initial burden is met does the burden of coming forward with evidence or argument shift to the Appellant. *Oetiker*, 977 F.2d at 1445, 24 USPQ2d at 1444.

Appellants respectfully submit that the combination of *Bram WO* and *Presta* fails to teach or suggest the presently claimed fusion proteins (or their use in the presently claimed methods) and fails to provide a reasonable expectation of success in achieving the presently claimed methods. For at least these reasons, Appellants submit that the

Examiner has failed to establish a *prima facie* case of unpatentability under 35 U.S.C. § 103(a).

A. The Combination of Bram WO and Presta Fails to Teach or Suggest the Presently Claimed Fusion Proteins

Appellants respectfully submit that the references of record fail to teach or suggest the presently claimed fusion proteins (or their use in the presently claimed methods). Claim 107, the only independent claim on appeal, is directed to methods using a fusion protein having a first portion consisting of a specific fragment of TACI (SEQ ID NO:6). Contrary to the Examiner's assertion, such a fusion protein is not taught by *Bram WO* (or *Presta*), nor is there any teaching in *Bram WO* (or *Presta*) which could lead one of ordinary skill in the art to such a fusion protein. Appellants respectfully submit that the Examiner has failed to make the underlying factual findings necessary to establish a *prima facie* case of unpatentability. In particular, the Examiner has failed to clearly articulate how one of ordinary skill in the art would arrive at the presently claimed TACI fragment based on these references. *Bram WO* provides a general disclosure and partial characterization of the TACI protein. Although brief reference is generically made to TACI fragments and TACI fusion proteins, with respect to the TACI extracellular domain only a single fragment consisting of the entire ~ 166 amino acid extracellular domain is specifically disclosed and only a single fusion protein, consisting of the ~ 166 amino acid extracellular domain fused to another peptide, is disclosed. There is no description of *any* sub-fragment of the TACI extracellular domain (or fusion protein containing same), much less the specifically claimed fragment consisting of amino acids 25-104 of SEQ ID NO: 6 (TACI). The presently claimed fragment, *corresponding to less than one-half the length of the TACI extracellular domain*, is simply not taught by *Bram*

WO, nor does *Bram WO* provide any suggestion that could lead one of ordinary skill in the art to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain respectively, to arrive at the presently claimed fragment. Therefore, *Bram WO* fails to teach or suggest making a fusion protein having a first portion consisting of amino acid residues 25-104 of TACI. The Examiner's position appears to be that because methods for making protein fragments were known, it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments until, by chance, the presently claimed fragment was produced. In other words, the Examiner bases his finding that the present claims are unpatentable on an "obvious to try" analysis. However, the claims on appeal are directed to methods using a fusion protein having a first portion consisting of a specific fragment of the TACI extracellular domain not taught or suggested by the prior art of record, not to methods for making TACI fragments. As discussed below, an "obvious to try" analysis is not proper in the present case.

i. *Principles of Law*

The U.S. Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007), found that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of **identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added). *Id.* at 1732. Thus, according to the Court, in certain limited situations, a *prima facie* case of obviousness may be predicated on an 'obvious to try' analysis. However, such an analysis is not proper unless: (1) the

solutions are identified, finite in number and predictable and (2) one of ordinary skill in the art could have pursued known solutions with a reasonable expectation of success. *Id.*

The Federal Circuit recently clarified the situations in which an 'obvious to try' analysis may be used to find patent claims obvious. In *Ortho-McNeil Pharmaceutical v. Mylan Labs*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), the Federal Circuit held that patent claims to a pharmaceutical were not obvious in view of the standard set forth in *KSR*. In reaching its decision, the Court found that, although a key ingredient of the invention may have been one of many a skilled artisan might have tried, evidence showed it was "not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness." Thus, the Court interpreted *KSR* as requiring that the number of options to be "small or easily traversed" in order to find a patent claim obvious under an "obvious to try" analysis. Moreover, the court referenced the need to avoid "hindsight", stating that the inventor's "pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Id.* The Court also emphasized that "a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case." *Id.*

In *In re Kubin*, 90 U.S.P.Q.2d 1417, 561 F.3d 1351 (Fed. Cir. 2009), the Federal Circuit clarified two classes of situations in which it is erroneous to equate "obvious to try" with obviousness. First, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness (emphasis added)." *Id* at 1423. According to the Court,

such cases are the inverse of the proposition set forth in *KSR* that obviousness may arise where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," *Id.* Second, the court clarified that an "obvious to try" analysis is impermissible in situations where the prior art does not guide an inventor toward a particular solution. In other words, an impermissible "obvious to try" situation occurs "where what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* Such cases express the same idea as the *KSR* requirement that the identified solutions be "predictable." In *Kubin*, the prior art disclosed a protein, a monoclonal antibody to the protein, and a routine method by which the DNA encoding the protein could be cloned. The Court found that an obvious to try analysis was proper because practicing the exact method disclosed in the prior art inevitably led to the single, precise DNA sequence discovered by the inventor. Because this was not a case where the skilled person was faced with combinatorial prior art possibilities and because the prior art inevitably led to a particular DNA sequence, the Court found the obvious to try analysis to be proper and affirmed the lower court's decision that claims covering the encoding DNA were obvious.

ii. *The Rejection of the Claims on Appeal under 35 U.S.C § 103(a) over Bram WO and Presta is Based on an Improper Application of the Law*

The Examiner acknowledges that *Bram WO* (and *Presta*) fails to describe (i.e. **identify**) any particular sub-fragment of the TACI extracellular domain, much less the presently claimed sub-fragment consisting of amino acid residues 25-104 of SEQ ID NO: 6. Nonetheless, the Examiner has found that it would have been obvious to the skilled

artisan to produce the specifically claimed fragment of the extracellular domain and test it for observed biological activity. In other words, the Examiner has found that because methods for making protein fragments were known, that it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments and test them for the ability to bind a then-unidentified ligand until, by chance, the presently claimed fragment was produced.

Such an analysis is contrary to the U.S. Supreme Court and Federal Circuit precedent discussed above. Indeed, the facts of the present case fit squarely within the class of cases for which *Kubin* forbids such an analysis. For a polypeptide of a given length, there is an inverse relationship between the number of potential fragments that can be constructed and the size of a given fragment. For a polypeptide of 166 amino acids (corresponding to the TACI extracellular domain disclosed by *Bram WO*), there are 157 ten-amino acid fragments, 156 eleven-amino acid fragments, 155 twelve-amino acid fragments and so forth. Excluding fragments below 10 amino acids, there are total of (157 + 156 + 155....+ 3 + 2) or 12,402 fragments. **Such is not a small or easily traversed number**. Even if one were to consider only fragments having 80 amino acids (corresponding in size to the claimed fragment consisting of amino acid residues 25-104), there are 87 possible 80-amino acid fragments of the TACI extracellular domain. In any event, the genus of potential fragments is vast and the prior art of record provides no guidance which could lead the skilled artisan to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively, to obtain the specifically claimed fragment. This is not a case where a skilled artisan could merely

pursue "known options" from a "finite number of identified, predictable solutions" nor can the vast genus of potential fragments be considered small and/or easily traversed.

Moreover, one of ordinary skill in the art has no way to predict from *Bram WO* which (if any) of the over twelve-thousand possible TACI extracellular fragments would constitute ztnf4-binding fragments. This is because *Bram WO* makes only a general statement that the ligand binding domain is located *somewhere within the TACI extracellular domain* (cite and again below) and does not identify ztnf4 or any other TACI ligand that could be used to determine which of the vast number of possible TACI extracellular fragments would retain ztnf4-binding capability. Indeed, based on the disclosure of *Bram WO*, one of ordinary skill in the art would have to test each TACI extracellular domain fragment for the ability to bind an unidentified ligand. Accordingly, it is clear that the "solutions" offered by *Bram WO* are unpredictable as well as neither small nor easily traversed. In this regard, Appellants present the following references demonstrating that, at the time of the present invention, it was unpredictable whether protein fragments comprising an extracellular ligand binding domain would retain ligand-binding function: Lin, J.C. *et al.*, Mol. Cell. Biol. 24(5):2041-2051 (2004) (*Lin*); Liapakis, G. *et al.*, J. Biol. Chem. 271(34):20331-20339 (1996) (*Liapakis*); Leiter, E.H. and Lee, C-H., Diabetes 54 (Suppl. 2):S151-S158 (2005) (*Leiter*); Excoffon, K. *et al.*, Am. J. Respir. Cell. Mol. Biol. 32:498-503 (2005) (*Excoffon*); and Wada A., *et al.*, Infect. Immun. 64(12):5144-5150 (1996) (*Wada*). A copy of each of these publications is provided under the Evidence Appendix. Predictability that the presently claimed fragment, which is missing 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively, would retain ligand-binding capability is

substantially further decreased. Because *Bram WO* fails to identify any ligand-binding fragment of the TACI extracellular domain or provide any guidance which could lead the skilled artisan to the specifically claimed fragment, the skilled artisan would have had to "throw metaphorical darts at a board filled with combinatorial prior art possibilities" in order to arrive at the presently claimed subject matter. Therefore, according to *Kubin*, the Examiner has failed to establish that the claimed subject matter is obvious.

The Examiner, at page 4 of the March 25 Advisory Action, states that *KSR* is the controlling case law with regard to 'obviousness'. However, the Examiner's analysis is improper in view of *KSR*, which limits application of the obvious to try analysis to cases where the prior art discloses a finite number of **identified, predictable solutions**. As discussed above, *Bram WO* fails to **identify** any particular TACI extracellular sub-fragment and there is simply no way to **predict** from *Bram WO* which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments.

At pages 4-5 of the March 25 Advisory Action, the Examiner attempts to distinguish the fact pattern in *Ortho-McNeil* from the present case. However, in *Ortho-McNeil* the Federal Circuit provided much-needed and universally applicable guidance to adjudicative bodies and regulatory agencies attempting to apply the principles set forth in *KSR*. The Examiner errs in attempting to limit the Court's guidance to the fact pattern of that case. As acknowledged by the Examiner, the Federal Circuit in *Ortho-McNeil* warned that the "obvious to try" analysis discussed in *KSR* is only properly applied in situations with a finite and in the context of the art, small and/or easily traversed number of options. As discussed above, the number of possible fragments of the TACI

extracellular domain is over **12,000**, which one of ordinary skill in the art would not consider to be a small **or** easily traversed number as alleged by the Examiner, particularly in view of the fact that TACI ligands were unknown at the priority date of the present application.

The disclosure of *Presta* does nothing to rectify the aforementioned failure of *Bram WO* to teach or suggest the specifically claimed fusion proteins.

Based on the aforementioned, it is clear that the Examiner has failed to make the requisite underlying factual findings as to how one of ordinary skill in the art could have arrived at the specifically claimed TACI fragment consisting of amino acids 25-104 of SEQ ID NO: 6 (or fusion proteins containing this fragment), and has improperly applied an "obvious to try" standard in finding the instant claims obvious over the cited prior art. Here, the prior art teaches generally that the ligand binding portion of TACI is located somewhere on the extracellular domain. The Examiner's contention that it would have been obvious to make and screen the multitude of fragments representing all possible overlapping peptides derived from the protein in order to find the specifically claimed ligand binding fragment is directly analogous to throwing "metaphorical darts at a board filled with combinatorial prior art possibilities" which, according to *Kubin*, cannot serve as the basis for finding claims 107-111 and 122-132 obvious. In this respect, it is clear that the Examiner has impermissibly used hindsight reconstruction to retrace the path of the present inventors and discounted the number of possible TACI extracellular domain sub-fragments. Thus, the pending claims are, as a matter of law, not obvious over the combination of *Bram WO* and *Presta* under 35 U.S.C. § 103(a) and it is respectfully

submitted that the Board of Patent Appeals and Interferences should reverse the rejection of claims 107-111 and 122-132 under 35 U.S.C. § 103(a).

B. The Combination of Bram WO and Presta Fails to Provide a Reasonable Expectation of Success

The Examiner has erred in finding that the combination of *Bram WO* and *Presta* provides a reasonable expectation of success in achieving the presently claimed methods. Whether the prior art provides a reasonable expectation of success is made at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Moreover, to "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 165 (Fed. Cir. 2006). Finally, a reasonable expectation of success requires more than where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular from of the claimed invention or how to achieve it." *Medichem*, 437 F.3d at 1167. The combination of *Bram WO* and *Presta* fails to provide any guidance that could lead one of ordinary skill in the art to reasonably expect that administration of the particularly claimed fusion protein would be effective in inhibiting B lymphocyte proliferation.

While obviousness does not require absolute predictability, at least some degree of predictability is required. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). As a corollary to this "predictability" requirement, the Federal Circuit, as recently as August 5, 2009, emphasized that:

> [The *O'Farrell* decision] observed that most inventions that are obvious are also obvious to try, but found two classes where that rule of thumb did not obtain.
>
> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421; *see also Procter & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that *KSR* requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where 'what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *O'Farrell*, 853 F.2d at 903. *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 91 USPQ2d 1569, 1572-73 (Fed. Cir. 2009).

Turning to the facts in the present case, the Examiner has alleged that "the number of possible deletion mutants encompassed by the instant claims is not only finite but easily traversed," and that the functionality of fusion proteins comprising such fragments "can be determined by determining B cell activation." March 25 Advisory Action, page 5. However, the Examiner has not pointed to any guidance in *Bram WO* as to particular sub-fragments of the TACI extracellular domain that would be likely to retain this ability. In the absence of such guidance, and in view of the unpredictability inherent in this art, one of ordinary skill in the art lacks a reasonable expectation of success that the presently claimed fragment, which is missing 24 and 62 amino acids

from the N- and C-termini of the TACI extracellular domain respectively, would bind ztnf4 and inhibit B lymphocyte proliferation, as required by the claims under appeal.

Contrary to the Examiner's assertion, one of ordinary skill in the art must resort to undue experimentation in order to arrive at the presently claimed fusion protein based on the disclosure of *Bram WO*. In order to arrive at the presently claimed invention, one of ordinary skill in the art would have to create literally *thousands* of fragments of the TACI extracellular domain, and test each fragment for the ability to inhibit B cell proliferation without the benefit of knowing the identity of any TACI ligand. Indeed, it is undisputed that *Bram WO* does not disclose any TACI ligand. Moreover, *Bram WO* fails to provide any working example demonstrating efficacy *in vivo* of any fusion protein containing any TACI fragment. Only through the present disclosure is one of ordinary skill taught the identity of ztnf4 as a ligand for the TACI receptor and the use of fusion proteins containing the presently claimed ztnf-binding sub-fragment of the TACI extracellular domain. Appellants respectfully submit that the Examiner's conclusion of obviousness amounts to impermissible hindsight reconstruction based on information gleaned from the present disclosure.

Presta, while teaching the fusion of the Fc fragment with other proteins to increase the circulating half-life, fails to remedy the aforementioned infirmities of *Bram WO*. As discussed above, *Bram WO* provides only a general approach to a promising field of experimentation and provides nothing more than general guidance as to how to achieve the presently claimed invention. Accordingly, for at least this reason, the combination of *Bram WO* and *Presta* fails to render the subject matter of the present claims obvious. It is therefore respectfully submitted that the Board of Patent Appeals

and Interferences should reverse the rejection of claims 107-111 and 122-132 under 35 U.S.C. § 103(a).

II. The Rejections Under 35 U.S.C. § 103(a) Over *Bram US* in View of *Presta* Are Improper and Should Be Withdrawn

The Examiner, in rejecting claims 107-111 and 122-132, alleges that *Bram US* teaches (1) genetically engineered constructs to regulate B-cell activity through interaction with cellular receptor ligands (2) that such constructs can consist of the extracellular domain of the TACI receptor linked by a peptide bond to the Fc domain of an immunoglobulin (3) that the extracellular domain of the TACI receptor has the amino acid sequence corresponding to about residue 1 to about residue 166 of the TACI sequence and (4) that the ligand binding region is a sub-fragment of the extracellular domain. Therefore, according to the Examiner, by utilizing the methods and materials disclosed by *Bram US*, "one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf is an endogenous ligand of TACI...Moreover, since the fusion proteins disclosed by Bram et al. are **identical** to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention." March 25 Advisory Action, pages 12-13 (emphasis added). According to the Examiner, *Bram US* fails to disclose the specific use of IgG1 heavy chains in fusion proteins or TACI extracellular sub-fragments consisting of amino acid residues 25-104 or 1-154 of SEQ ID NO:6 in fusion proteins. The Examiner refers to *Presta* as disclosing "methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)." According to the Examiner:

> ...given that there (sic) Bram discloses the use of the full length TACI extracellular domain (SEQ ID NO:6) and that there are a finite number of

> fragments of said extracellular domain and (sic) it would have been obvious to the skilled artisan to produce said fragments in order to identify the specific binding domain (fragment) of the TACI extracellular domain responsible for the observed biological activity (i.e. modulating B cell proliferation/activity). The skilled person would have had a reasonable expectation of success as the generation of protein fragments to identify biologically active domains...It would have been obvious for one of ordinary skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. March 25 Advisory Action, pages 13-14.

Appellants respectfully submit that the combination of *Bram US* and *Presta* fails to teach or suggest the presently claimed fragments (or their use in the presently claimed methods) and fails to provide a reasonable expectation of success in achieving the presently claimed methods. For at least these reasons, Appellants submit that the Examiner has failed to establish a *prima facie* case of unpatentability under 35 U.S.C. § 103(a).

A. The Combination of Bram US and Presta Fails to Teach or Suggest the Presently Claimed Fusion Proteins

Appellants respectfully submit that the references of record fail to teach or suggest the presently claimed fragments (or their use in the presently claimed methods). Claim 107, the only independent claim on appeal, is directed to methods using a fusion protein having a first portion consisting of a specific fragment of TACI (SEQ ID NO:6). Contrary to the Examiner's assertion, such a fusion protein is not taught by *Bram US* (or

Presta), nor is there any teaching in *Bram US* (or *Presta*) which could lead one of ordinary skill in the art to such a fusion protein. Appellants respectfully submit that the Examiner has failed to make the underlying factual findings necessary to establish a *prima facie* case of unpatentability. In particular, the Examiner has failed to clearly articulate how one of ordinary skill in the art would arrive at the presently claimed TACI fragment based on these references. *Bram US* provides a general disclosure and partial characterization of the TACI protein. Although brief reference is generically made to TACI fragments and TACI fusion proteins, with respect to the TACI extracellular domain only a single fragment consisting of the entire ~ 166 amino acid extracellular domain is specifically disclosed and only a single fusion protein consisting of the ~ 166 amino acid extracellular domain fused to another peptide is disclosed. There is no disclosure of *any* sub-fragment of the TACI extracellular domain (or fusion protein containing same), much less the specifically claimed fragment consisting of amino acids 25-104 of SEQ ID NO: 6 (TACI). The presently claimed fragment, *corresponding to less than one-half the length of the TACI extracellular domain*, is simply not taught by *Bram US*, nor does *Bram US* provide any suggestion that could lead one of ordinary skill in the art to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively to arrive at the presently claimed fragment. Therefore, *Bram US* cannot provide motivation to the skilled artisan to make fusion proteins containing the specifically claimed fragment. The Examiner's position appears to be that because methods for making protein fragments were known, it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments until, by chance, the presently claimed fragment was produced. In other words, the Examiner bases his

finding that the present claims are unpatentable on an "obvious to try" analysis. However, the claims on appeal are directed to methods using a fusion protein having a first portion consisting of a specific fragment of the TACI extracellular domain not taught or suggested by the prior art of record, not to methods for making TACI fragments. As discussed below, an "obvious to try" analysis is not proper in the present case.

i. *The Rejection of the Claims on Appeal under 35 U.S.C § 103(a) over Bram US and Presta is Based on an Improper Application of the Law*

The Examiner acknowledges that *Bram US* (and *Presta*) fails to disclose (i.e. **identify**) any particular sub-fragment of the TACI extracellular domain, much less the presently claimed sub-fragment consisting of amino acid residues 25-104 of SEQ ID NO: 6. Nonetheless, the Examiner has found that it would have been obvious to the skilled artisan to produce the specifically claimed fragment of the extracellular domain and test it for observed biological activity. In other words, the Examiner has found that because methods for making protein fragments were known, that it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments and test them for the ability to bind a then-unidentified ligand until, by chance, the presently claimed fragment was produced.

Such an analysis is contrary to the U.S. Supreme Court and Federal Circuit precedent discussed above. Indeed, the facts of the present case fit squarely within the class of cases for which *Kubin* forbids such an analysis. For a polypeptide of a given length, there is an inverse relationship between the number of potential fragments that can be constructed and the size of a given fragment. For a polypeptide of 166 amino acids (corresponding to the TACI extracellular domain disclosed by *Bram US*), there are 157 ten-amino acid fragments, 156 eleven-amino acid fragments, 155 twelve-amino acid

fragments and so forth. Excluding fragments below 10 amino acids, there are total of (157 + 156 + 155....+ 3 + 2) or 12,402 fragments. Such is not a small or easily traversed number. Even if one were to consider only fragments having 80 amino acids (corresponding in size to the claimed fragment consisting of amino acid residues 25-104), there are 87 possible 80-amino acid fragments of the TACI extracellular domain. In any event, the genus of potential fragments is vast and the prior art of record provides no guidance which could lead the skilled artisan to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively, to obtain the specifically claimed fragment. This is not a case where a skilled artisan could merely pursue "known options" from a "finite number of identified, predictable solutions" nor can the vast genus of potential fragments be considered small and/or easily traversed.

Moreover, one of ordinary skill in the art has no way to predict from *Bram US* which (if any) of the over twelve-thousand possible TACI extracellular fragments would constitute ztnf4-binding fragments. This is because *Bram US* makes only a general statement that the ligand binding domain is located *somewhere within the TACI extracellular domain* (cite) and does not identify ztnf4 or any other TACI ligand that could be used to determine which of the vast number of possible TACI extracellular fragments would retain ztnf4-binding capability. Indeed, based on the disclosure of *Bram US*, one of ordinary skill in the art would have to test each TACI extracellular domain fragment for the ability to bind an unidentified ligand. Accordingly, it is clear that the "solutions" offered by *Bram US* are unpredictable as well as neither small nor easily traversed. In this regard, *Lin*, *Liapakis*, *Leiter*, *Excoffon*, and *Wada* provide evidence that it was unpredictable whether protein fragments comprising an extracellular ligand

binding domain would retain ligand-binding function. Predictability that the presently claimed fragment, which is missing 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively, would retain ligand-binding capability is substantially further decreased. Because *Bram US* fails to identify any ligand-binding fragment of the TACI extracellular domain or provide any guidance which could lead the skilled artisan to the specifically claimed fragment, the skilled artisan would have had to "throw metaphorical darts at a board filled with combinatorial prior art possibilities" in order to arrive at the presently claimed subject matter. Therefore, according to *Kubin*, the Examiner has failed to establish that the claimed subject matter is obvious.

The Examiner, at page 10 of the March 25 Advisory Action, states that *KSR* is the controlling case law with regard to 'obviousness'. However, the Examiner's analysis is improper in view of *KSR*, which limits application of the obvious to try analysis to cases where the prior art discloses a finite number of **identified, predictable solutions**. As discussed above, *Bram US* fails to **identify** any TACI extracellular sub-fragment and there is simply no way to **predict** from *Bram US* which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments.

At pages 10-11 of the March 25 Advisory Action, the Examiner attempts to distinguish the fact pattern in *Ortho-McNeil* from the present case. However, in *Ortho-McNeil* the Federal Circuit provided much-needed and universally applicable guidance to adjudicative bodies and regulatory agencies attempting to apply the principles set forth in *KSR*. The Examiner errs in attempting to limit the Court's guidance to the fact pattern of that case. As acknowledged by the Examiner, the Federal Circuit in *Ortho-McNeil* warned that the "obvious to try" analysis discussed in *KSR* is only properly applied in

situations with a finite and in the context of the art, small and/or easily traversed number of options. As discussed above, the number of possible fragments of the TACI extracellular domain is over **12,000**, which one of ordinary skill in the art would not consider to be a small **or** easily traversed number as alleged by the Examiner, particularly in view of the fact that TACI ligands were unknown at the priority date of the present application.

The disclosure of *Presta* does nothing to rectify the aforementioned failure of *Bram US* to teach or suggest the specifically claimed fusion proteins.

Based on the aforementioned, it is clear that the Examiner has failed to make the requisite underlying factual findings as to how one of ordinary skill in the art could have arrived at the specifically claimed TACI fragment consisting of amino acids 25-104 of SEQ ID NO: 6 (or fusion proteins containing this fragment), and has improperly applied an "obvious to try" standard in finding the instant claims obvious over the cited prior art. Here, the prior art teaches generally that the ligand binding portion of TACI is located somewhere on the extracellular domain. The Examiner's contention that it would have been obvious to make and screen the multitude of fragments representing all possible overlapping peptides derived from the protein in order to find the specifically claimed ligand binding fragment is directly analogous to throwing "metaphorical darts at a board filled with combinatorial prior art possibilities" which, according to *Kubin*, cannot serve as the basis for finding claims 107-111 and 122-132 obvious. In this respect, it is clear that the Examiner has impermissibly used hindsight reconstruction to retrace the path of the present inventors and discounted the number of possible TACI extracellular domain sub-fragments. Thus, the pending claims are, as a matter of law, nonobvious over the

combination of *Bram US* and *Presta* under 35 U.S.C. § 103(a) and it is respectfully submitted that the Board of Patent Appeals and Interferences should reverse the rejection of claims 107-111 and 122-132 under 35 U.S.C. § 103(a).

B. The Combination of Bram US and Presta Fails to Provide a Reasonable Expectation of Success

The Examiner has erred in finding that the combination of *Bram US* and *Presta* provides a reasonable expectation of success in achieving the presently claimed methods. The combination of *Bram US* and *Presta* fails to provide any guidance that could lead one of ordinary skill in the art to reasonably expect that administration of the claimed fusion protein would be effective in inhibiting B lymphocyte proliferation.

The Examiner has alleged that "the number of possible deletion mutants encompassed by the instant claims is not only finite but easily traversed," and that the functionality of fusion proteins comprising such fragments "can be determined by determining B cell activation." March 25 Advisory Action, page 11. However, the Examiner has not pointed to any guidance in *Bram US* as to particular sub-fragments of the TACI extracellular domain that would be likely to retain this ability. In the absence of such guidance, and in view of the unpredictability inherent in this art, one of ordinary skill in the art lacks a reasonable expectation of success that the presently claimed fragment, which is missing 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain respectively, would bind ztnf4 and inhibit B lymphocyte proliferation, as required by the claims under appeal.

Contrary to the Examiner's assertion, one of ordinary skill in the art must resort to undue experimentation in order to arrive at the presently claimed fusion protein based on the disclosure of *Bram US*. In order to arrive at the presently claimed invention, one of

ordinary skill in the art would have to create literally *thousands* of fragments of the TACI extracellular domain, and test each fragment for the ability to inhibit B cell proliferation without the benefit of knowing the identity of any TACI ligand. Indeed, it is undisputed that *Bram US* does not disclose any TACI ligand. Moreover, *Bram US* fails to provide any working example demonstrating efficacy *in vivo* of any fusion protein containing any TACI fragment. Only through the present disclosure is one of ordinary skill taught the identity of ztnf4 as a ligand for the TACI receptor and the use of fusion proteins containing the presently claimed ztnf-binding sub-fragment of the TACI extracellular domain. Appellants respectfully submit that the Examiner's conclusion of obviousness amounts to impermissible hindsight reconstruction based on information gleaned from the present disclosure.

Presta, while teaching the fusion of the Fc fragment with other proteins to increase the circulating half-life, fails to remedy the aforementioned infirmities of *Bram US*. As discussed above, *Bram US* provides only a general approach to a promising field of experimentation and provides nothing more than general guidance as to how to achieve the presently claimed invention. Accordingly, for at least this reason, the combination of *Bram US* and *Presta* fails to render the subject matter of the present claims obvious. It is therefore respectfully submitted that the Board of Patent Appeals and Interferences should reverse the rejection of claims 107-111 and 122-132 under 35 U.S.C. § 103(a).

8. Conclusion

For all the reasons provided above, Appellants respectfully submit that the rejections of claims 107-111 and 117-132 under 35 U.S.C. § 103(a) over *Bram WO* in view of *Presta* and over *Bram US* in view of *Presta*, are in error and thus, the rejections may be properly reversed by the Board of Patent Appeals and Interferences, and such reversal is supported by the applicable patent law.

Respectfully submitted,
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Appendix of Claims (37 CFR 41.37(c))

107. A method of inhibiting B lymphocyte proliferation in a mammal, comprising administering to the mammal a composition comprising a fusion protein that consists of a first portion and a second portion, wherein the first portion and the second portion are joined by a peptide bond, wherein the first portion of the fusion protein consists of the amino acid sequence of amino acid residues 25 to 104 of SEQ ID NO:6 wherein the second portion of the fusion protein is an immunoglobulin heavy chain constant region and wherein the fusion protein binds ztnf4.

108. The method of claim 107, wherein the immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region.

109. The method of claim 108, wherein the human immunoglobulin heavy chain constant region is a human immunoglobulin heavy chain constant region of IgG1.

110. The method of claim 107, wherein the composition comprises multimeric proteins comprising one or more polypeptide fusions.

111. The method of claim 110, wherein the composition comprises dimeric proteins comprising one or more polypeptide fusions.

122. The method of claim 107, wherein said B lymphocyte proliferation is associated with an autoimmune disease.

123. The method of claim 122, wherein said autoimmune disease is systemic lupus erythematosus, myasthenia gravis, multiple sclerosis or rheumatoid arthritis.

124. The method of claim 107, wherein said B lymphocyte proliferation is associated with bronchitis, emphysema or end stage renal failure.

125. The method of claim 107, wherein said B lymphocyte proliferation is associated with renal disease.

126. The method of claim 125, wherein said renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis.

127. The method of claim 107, wherein said B lymphocyte proliferation is associated with renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis.

128. The method of claim 107, wherein said inhibiting B lymphocyte proliferation is associated with regulation of immune response.

129. The method of claim 107, wherein said inhibiting B lymphocyte proliferation is associated with immunosuppression.

130. The method of claim 129, wherein said immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation.

131. The method of claim 130, wherein said autoimmune disease is insulin dependent diabetes mellitus or Crohn's Disease.

132. The method of claim 130, wherein said inflammation is associated with joint pain, swelling, anemia or septic shock.

Evidence Appendix (37 CFR 41.37(c))

1. Bram *et al.*, WIPO Publication No. WO 98/39361. This document appears throughout the record including the Office Actions dated August 18, 2008, February 11, 2009, and October 27, 2009, Submission Accompanying Request for Continued Examination dated November 10, 2008 and Amendment and Reply dated August 11, 2009.

2. Presta *et al.*, U.S. Patent No. 5,739,277. This document appears throughout the record including the Office Actions dated August 18, 2008, February 11, 2009, and October 27, 2009, Submission Accompanying Request for Continued Examination dated November 10, 2008 and Amendment and Reply dated August 11, 2009.

3. Bram *et al.*, U.S. Patent No. 5,969,102. This document appears throughout the record including the Office Actions dated August 18, 2008, February 11, 2009, and October 27, 2009, Submission Accompanying Request for Continued Examination dated November 10, 2008 and Amendment and Reply dated August 11, 2009.

4. Lin, J.C. *et al.*, Mol. Cell. Biol. 24(5):2041-2051 (2004), entered into the record by Examiner in an attachment to non-final Office Action dated February 11, 2009.

5. Liapakis, G. *et al.*, J. Biol. Chem. 271(34):20331-20339 (1996), entered into the record by Examiner in an attachment to non-final Office Action dated February 11, 2009.

6. Leiter, E.H. and Lee, C-H., Diabetes 54 (Suppl. 2):S151-S158 (2005), entered into the record by Examiner in an attachment to non-final Office Action dated February 11, 2009.

7. Excoffon, K. *et al.*, Am. J. Respir. Cell. Mol. Biol. 32:498-503 (2005), entered into the record by Examiner in an attachment to non-final Office Action dated February 11, 2009.

8. Wada A., *et al.*, Infect. Immun. 64(12):5144-5150 (1996), entered into the record by Examiner in an attachment to non-final Office Action dated February 11, 2009.

Related Proceedings Appendix (37 CFR 41.37(c))

No decisions have been rendered by a court or the Board in any related proceeding.